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Critical review of current clinical practice guidelines for antifungal therapy in paediatric haematology and oncology

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Abstract

Purpose The incidence of invasive fungal disease (IFD) is rising, but its treatment in paediatric haematology and oncology patients is not yet standardised. This review aimed to critically appraise and analyse the clinical practice guidelines (CPGs) that are available for paediatric IFD.

Methods Electronic searches of MEDLINE, MEDLINE in-Process & Other non-Indexed Citations, the Guidelines International Network (GIN), guideline.gov and Google were performed and combined fungal disease (Fung* OR antifung*OR Candida* OR Aspergill*) with prophylaxis or treatment (prophyl* OR therap* OR treatment). All guidelines were assessed using the AGREE II tool and recommendations relating to prophylaxis, empirical treatment and specific therapy were extracted.

Results Nineteen guidelines met the inclusion criteria. The AGREE II scores for the rigour of development domain ranged from 11 to 92 % with a median of 53 % (interquartile range 32–69 %). Fluconazole was recommended as antifungal prophylaxis in all nine of the included guidelines which recommended a specific drug. Liposomal amphotericin B was recommended in all five guidelines giving empirical therapy

recommendations. Specific therapy recommendations were given for oral or genital candidiasis, invasive candida infection, invasive aspergillosis and other mould infections.

Conclusions In many areas, recommendations were clear about appropriate practice but further clarity was required, particularly relating to the decision to discontinue empirical antifungal treatment, the relative benefits of empiric and pre-emptive strategies and risk stratification.

Future CPGs could consider working to published guideline production methodologies and sharing summaries of evidence appraisal to reduce duplication of effort, improving the quality and efficiency of CPGs in this area.

Keywords Fungal infection · Paediatric · Guideline · Critical review

Abbreviations

AGIHO	Infectious Diseases Working Party
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
CPGs	Clinical practice guidelines
DGHO	German Society of Hematology and Oncology
ECIL-4	Fourth European Conference on Infections in Leukaemia
ECMM	European Confederation of Medical Mycology
EORTC/	European Organisation for Research and
MSG	Treatment of Cancer Mycoses Study Group
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
GIN	Guidelines International Network
GITMO	Gruppo Italiano Trapianto Midollo Osseo
HSCT	Haematopoietic stem cell transplant
IDSA	Infectious Diseases Society of America
IFD	Invasive fungal disease

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IOM	Institute of Medicine
SEIMC	Spanish Society of Infectious Diseases and Clinical Microbiology
SIGN	Scottish Intercollegiate Guidelines Network

Background

Invasive fungal disease (IFD) describes tissue damage associated with clinical illness as a result of infection with yeast or mould. The incidence of IFD is rising, perhaps related to more intensive immunosuppression in the treatment of patients with a variety of conditions as well as improved survival of those with inherited immunodeficiencies [1]. Meanwhile, deaths due to IFD in the USA rose from 0.13 to 0.21 per 100,000 population in 0–4 year olds and from 0.13 to 0.31 per 100,000 population in 5–24 year olds between 1980 and 1997 [1].

Within paediatrics, the patients most commonly affected by IFD are those with haematological malignancy (particularly acute myeloid leukaemia and relapsed acute lymphoblastic leukaemia), those undergoing allogeneic haematopoietic stem cell transplant (HSCT) and those receiving highly myelosuppressive chemotherapy for other malignancies [2]. The outcome of IFD with current therapies is poor. Yeast infections, including *Candida*, are associated with mortality of 10–50 %. Invasive *Aspergillus* is even more challenging with 52.5–85 % mortality [3–5].

The treatment of IFD is not yet standardised. A recent review of practice in multiple clinical centres found that the prophylactic therapy administered for paediatric IFD varies widely [6]. This may be due, in part, to regional variations in the epidemiology of IFD resulting in different antifungal susceptibility patterns. However, it may also be related to minimal available trial data on the use of antifungal agents in paediatric patients leading to the extrapolation of outcomes from adult studies. For this reason, the pharmacokinetic and pharmacodynamic properties of many antifungal agents in children are undefined. Furthermore, the spectrum of antifungal coverage, side effect profile, and interactions with other medications varies, which results in no clear choice of first-line antifungal treatment [7].

Given these treatment challenges in paediatric IFD, institutions have created clinical practice guidelines (CPGs) to help physicians manage this group of patients. CPGs are statements compiled following a systematic search of the evidence to assist healthcare practitioners in making decisions about individual patients based on the best available research combined with clinical expertise. Through systematic research and development, a core of key principles have been derived which delineate high-quality guidelines, leading to guideline creation manuals from the National Institute for Health and Clinical Excellence (NICE) in England and Wales, the US Institute of

Medicine (IOM) and the Scottish Intercollegiate Guidelines Network (SIGN).

We anticipated that some guidelines included in this review might have been less thorough in their approach to systematically reviewing the literature and compiling the evidence to support their recommendations. Thus, although we use the acronym CPGs throughout this review, readers should note that some guidelines may not fully meet the stringent criteria of an ideal CPG. The assessment of the recommendation production process and the quality of guidelines was felt to be an essential part of this review and informs the results and conclusions drawn.

The AGREE II tool is an appraisal tool developed to assess the quality of guidelines and consists of 23 items [8]. The items are grouped within six domains to provide key areas for guideline development. These domains are scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. Guidelines should be scored on each item by independent assessors using a seven-point Likert scale where 1 represents a poor score and 7 represents excellent demonstration of key quality criteria. The item scores are then combined to give scaled domain scores in percentages. Assessors are also requested to provide an opinion on whether they would recommend the assessed guideline for clinical use. The AGREE II tool, and further information on its development and application, is available from www.agreetrust.org. An overview of the items and domains is given within Table 1.

This review aimed to examine the clinical practice guidelines (CPGs) that are available for paediatric IFD. It aimed to assess the quality of guidance available to paediatric haematology and oncology teams. From this, we aimed to determine whether resources should be directed towards developing new or improved guidance or on the implementation of CPGs that are already in circulation.

Methods

Searches

A protocol for the review was developed prior to commencing the work. Electronic searches of MEDLINE, MEDLINE in-Process & Other non-Indexed Citations, the Guidelines International Network (GIN), guideline.gov and Google (first 200 Google results only) were performed in September 2013, combining fungal disease (Fung* OR antifung* OR Candida* OR Aspergill*) with prophylaxis or treatment (prophyl* OR therap* OR treatment). Within MEDLINE, searches were limited to ‘Guideline’ within the Article Type. Experts in the field were contacted asking for further potential guidelines. An updated search was performed in September 2015.

Table 1 The AGREE II tool items and domains [8]

Domain	Items
Scope and purpose	<ol style="list-style-type: none"> 1. The overall objective(s) of the guideline is (are) specifically described. 2. The health question(s) covered by the guideline is (are) specifically described. 3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Stakeholder involvement	<ol style="list-style-type: none"> 4. The guideline development group includes individuals from all relevant professional groups. 5. The views and preferences of the target population (patients, public, etc.) have been sought. 6. The target users of the guideline are clearly defined.
Rigour of development	<ol style="list-style-type: none"> 7. Systematic methods were used to search for evidence. 8. The criteria for selecting the evidence are clearly described. 9. The strengths and limitations of the body of evidence are clearly described. 10. The methods for formulating the recommendations are clearly described. 11. The health benefits, side effects, and risks have been considered in formulating the recommendations. 12. There is an explicit link between the recommendations and the supporting evidence. 13. The guideline has been externally reviewed by experts prior to its publication. 14. A procedure for updating the guideline is provided.
Clarity of presentation	<ol style="list-style-type: none"> 15. The recommendations are specific and unambiguous. 16. The different options for management of the condition or health issue are clearly presented. 17. Key recommendations are easily identifiable.
Applicability	<ol style="list-style-type: none"> 18. The guideline describes facilitators and barriers to its application. 19. The guideline provides advice and/or tools on how the recommendations can be put into practice. 20. The potential resource implications of applying the recommendations have been considered. 21. The guideline presents monitoring and/or auditing criteria.
Editorial independence	<ol style="list-style-type: none"> 22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed.

Inclusion

Guidelines regarding antifungal prophylaxis or treatment of established fungal infection or both were included. A decision was made not to include a reference to paediatrics within the search criteria as it was recognised that many paediatric guidelines could be embedded within adult guidelines. When screening for inclusion to this review, only those guidelines with explicit recommendations for paediatric patients were included. Furthermore, no search criteria relating to haematology, oncology or malignancy was included as guidelines for these patients may be included within more generalised guidelines about antifungal therapies. Only those guidelines which explicitly state that they are intended for use in patients with haematological and oncological diagnoses were included in this review. Only guidelines with acknowledgement from a producing body which had been published formally or deposited in an accredited repository were considered. Only English language guidelines were included. No

date limitations were applied. The most up-to-date published version of each guideline was included.

Study selection

One researcher reviewed all titles for those clearly not relevant, with a low threshold for including within the review. Two reviewers screened the abstracts of all studies for inclusion. Full text was obtained for all potential articles of interest. All full texts were assessed for eligibility by two reviewers. Disagreements were resolved by consensus or referred to a third reviewer (RP).

Quality assessment and data extraction

The quality of all guidelines was assessed using the AGREE II criteria by two researchers [8]. General data were collected for each included guideline, including producing body, funding source and the intended audience. The recommendations of

each guideline were extracted and then the data iteratively analysed. Key elements of inconsistency were explored, relating these areas to quality of development, health care system within which the guideline was developed and the evidence from which the recommendation was derived. The rigour of development domain was considered the key descriptor of quality, as this domain assesses the description of the methods of searching, selecting and combining evidence in the creation of the guidelines. Guidelines with an AGREE II development score of GOOD (defined as a scaled domain score of 65 % on 4 or more domains, which had to include ‘Rigour of Development’ and ‘Clarity of Presentation’) were examined to establish whether this group provide different guidance to those with poorer development scores.

Results

Guideline details

Initial searches, including 930 entries (after removal of duplicates), were sifted for titles which were clearly not relevant. Eighty-four abstracts were assessed in detail, with 32 full text articles retrieved and one additional guideline identified after contacting experts. Fourteen of these were included in the final analysis (see Fig. 1). Five further guidelines were identified by the updated search in September 2015, bringing the total number of included guidelines to 19. Information on excluded guidelines is given in Online Resource 2, and general information for each included guideline in Online Resource 3.

Ten guidelines provided recommendations on prophylaxis against fungal disease [9–18], five presented recommendations for empirical treatment [10, 11, 15, 16, 19] and 13 gave guidance on the management of specific fungal infections [9, 11, 15, 17, 19–27]. The majority guidelines come from North America and Europe, with one each from Australasia and Asia.

Quality assessment

Individual AGREE II domain scores for each guideline along with median and interquartile ranges for each domain are given in Online Resource 4. The scores for the rigour of development domain ranged from 11 to 92 % with a median of 53 % (interquartile range 32–69 %). This is somewhat poorer than the rigour of development seen in guidelines in other areas of Paediatric Haematology and Oncology [28]. In other domains, the scope and purpose and clarity of presentation domains generally scored highly, with stakeholder involvement and editorial independence domains being much more variable. The applicability domain generally scored poorly,

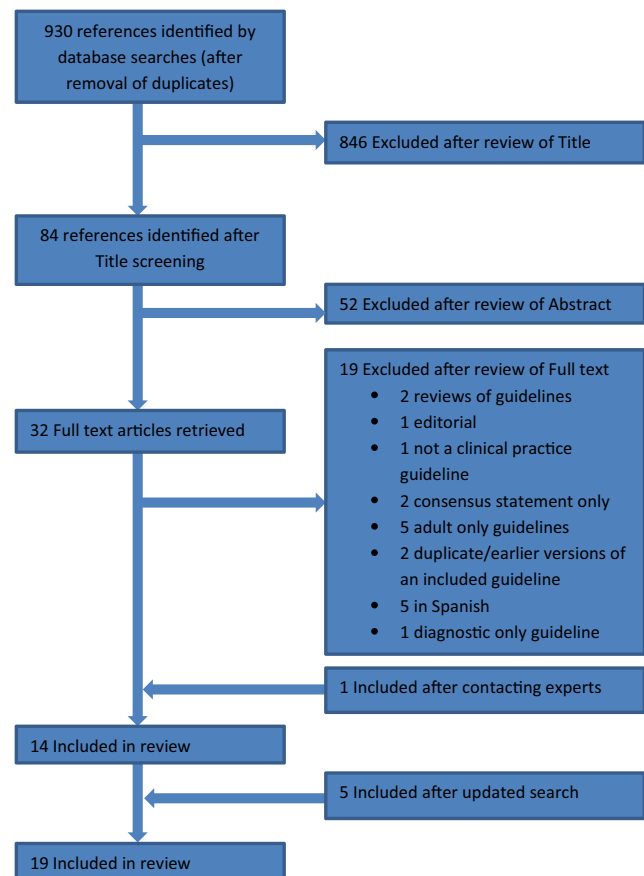


Fig. 1 Flow diagram for guideline selection

with minimal consideration given to how to implement their recommendations into practice.

Only two guidelines received an AGREE II development score of GOOD [13, 24]. One of these was a focused guideline on confirmed sporotrichosis and therefore contributes little to the other aspects of this review [24]. The other GOOD guideline was the C17 guideline which addresses primary antifungal prophylaxis in children with cancer [13]. Generally, the other, poorer quality guidelines gave recommendations that are consistent with the C17 work. However, there was disagreement over the use of prophylaxis in early phases of ALL treatment, where the C17 guideline did not recommend prophylaxis use, in contrast to other included guidelines.

Analysis

The main recommendations from the guidelines are summarised in Table 2, with the recommendations from GOOD quality guidelines highlighted in *italics*.

Prophylaxis

Education about dietary and environmental risk factors for invasive fungal disease was advised by two of the guidelines, and

Table 2 Summary of guideline recommendations

	Recommendations
Prophylaxis	
Primary prophylaxis recipients	<ul style="list-style-type: none"> • <i>Allogeneic HSCT—eight guidelines</i> [9–15, 18] • <i>Autologous stem cell return—seven guidelines</i> [9, 10, 12–16] • <i>AML and relapsed leukaemia—five guidelines</i> [10–14] • Early phases of ALL—four guidelines [9–11, 14] • <i>NOT early phases of ALL—one guideline</i> [13]
Primary prophylaxis drugs	<ul style="list-style-type: none"> • <i>Fluconazole—nine guidelines</i> [9–16, 18] • Liposomal amphotericin B—four guidelines [10, 11, 14, 15] • Itraconazole—six guidelines [10–12, 14, 15, 18] • <i>Posaconazole—seven guidelines</i> [9–14, 18] • Voriconazole—four guidelines [10–12, 18] • Micafungin—four guidelines [10–12, 18] • Caspofungin—one guideline [9]
Duration	<ul style="list-style-type: none"> • <i>Until neutrophil count recovery—eight guidelines</i> [9–16] • Day 0 to day 75 in allogeneic HSCT—two guidelines [10, 18] • Until steroid dose <0.5 mg/kg/day of prednisolone—one guideline [14]
Empirical and pre-emptive therapy	
Drugs advised	<ul style="list-style-type: none"> • Liposomal amphotericin B—five guidelines [9–11, 15, 16, 19] • Caspofungin—three guidelines [9, 11, 15] • Itraconazole—two guidelines [9, 15] • Voriconazole—two guidelines [9, 15] • Fluconazole (when not used for prophylaxis)—three guidelines [9, 15, 19]
Initiation	<ul style="list-style-type: none"> • Persistent febrile neutropenia, without a clear source, after 4 days of broad-spectrum antibiotic therapy—two guidelines [11, 15]
Duration	<ul style="list-style-type: none"> • Resolution of granulocytopenia in absence of suspected or documented IFD—one guideline [11] • Reassess and consider after 48–72 h—one guideline [15]
Specific therapies	
Candida	<ul style="list-style-type: none"> • Remove all central lines—five guidelines [9, 11, 19, 20, 25] • Use fluconazole, an echinocandin or high-dose amphotericin B—five guidelines [9, 11, 15, 19, 25] • Duration—at least 14 days from last positive, or first negative, blood culture—four guidelines [9, 11, 19, 25]
Invasive aspergillosis	<ul style="list-style-type: none"> • Use voriconazole or high-dose liposomal amphotericin B—three guidelines [11, 15, 19] • Echinocandins are an acceptable alternative—three guidelines [11, 15, 19] • Duration dependent on response and immunological recovery—one guideline [19]

Recommendations consistent with the C17 guidelines are in italics

HSCT haematopoietic stem cell transplant, AML acute myeloid leukaemia, ALL acute lymphoblastic lymphoma

specific details of their recommendations included in each [12, 14]. Topical treatments (including nystatin and clotrimazole) were not advised for the prevention of invasive fungal disease in any guideline except the Taiwanese guideline [12, 15, 16].

The included guidelines which mentioned prophylaxis were clear that all allogeneic transplant recipients should receive antifungal prophylaxis during their neutropenia [9–15, 18]. Those guidelines that mentioned patients receiving autologous stem cell return also advised prophylaxis for this group [9, 10,

12–16]. Similarly, many guidelines recommended prophylaxis for those with AML and relapsed leukaemia; the other guidelines did not specifically comment on these groups [10–14]. Recommendations for prophylaxis in the early phases of treatment for ALL, specifically in induction, were less clear, with four guidelines recommending prophylaxis [9–11, 14] whilst the C17 Council advised that it was not required. [13].

Fluconazole was recommended as anti-yeast prophylaxis in all nine of the included guidelines which recommended a

specific drug [9–16, 18]. Liposomal amphotericin B was named as an appropriate alternative agent in four of these guidelines [10, 11, 14, 15], itraconazole in six [10–12, 14, 15, 18], posaconazole in seven [9–14, 18], voriconazole in four [10–12, 18], micafungin in four [10–12, 18] and caspofungin in one [9]. Therapeutic drug monitoring when using itraconazole was advised in three guidelines [10, 11, 18].

The duration of prophylaxis advised by included guidelines universally recommended continuation until neutrophil count recovery (to $>1.0 \times 10^9/\text{L}$ where specified) [9–16]. The ESCMID and GITMO guidelines recommended prophylaxis from day 0 to day 75 in allogeneic HSCT recipients [10, 18]. The SEIMC guidelines recommended continuation of antifungal prophylaxis until the steroid dose was $<0.5 \text{ mg/kg/day}$ of prednisolone [14].

Secondary prophylaxis is a term often used to describe ongoing treatment or prophylaxis against further fungal infection following a previous episode of IFD. Two guidelines gave recommendations about secondary prophylaxis. One recommended a mould-active drug, potentially voriconazole, following previous invasive aspergillosis; the other recommended ongoing treatment until the patient was immunocompetent, but did not give further guidance about this aspect of IFD management [11, 12].

Empirical and pre-emptive therapy

Empirical treatment is that which is initiated when a physician suspects IFD in a high-risk patient, in particular a child with prolonged febrile neutropenia, but has no diagnostic evidence for IFD, whilst pre-emptive treatment describes the use of antifungal agents in patients with probable IFD whilst awaiting diagnostic results, as per EORTC/MSG definitions [29]. The guidelines included in this review generally provided empirical treatment recommendations which are described in this appraisal. The ECIL-4 guidelines recommended that pre-emptive treatment strategies may be appropriate for certain children in facilities where rapid results of diagnostic tests are available; no other guideline provided guidance on pre-emptive treatment [11].

Liposomal amphotericin B was recommended in all five guidelines giving empirical therapy recommendations [9–11, 15, 16, 19]. This was based on equal efficacy, reduced number of breakthrough infections, reduced infusion related toxicity and reduced nephrotoxicity compared with other agents [16, 19]. Caspofungin was given as an acceptable alternative in the IDSA, ECIL-4 and Taiwanese guidelines [9, 11, 15]. Itraconazole or voriconazole were stated as appropriate alternatives by two guidelines [9, 15]. Where fluconazole prophylaxis had not been administered, the IDSA, Australasian and Taiwanese guidelines recommended that fluconazole could be used for empirical treatment [9, 15, 19].

Where indications for initiating treatment were given, these advised the introduction of empirical antifungals if there is

persistent febrile neutropenia, without a clear source, after 4 days of treatment with broad-spectrum antibacterial therapy [11, 15]. There were few recommendations about when to stop empirical antifungal therapy. ECIL-4 guidelines suggested on “resolution of granulocytopenia in the absence of suspected or documented IFD” [11] whilst the Taiwanese guidelines advised reassessment and possible discontinuation after 48–72 h [15].

Specific therapy

Invasive candida infection All guidelines covering invasive candida infections recommended the removal of all central lines, if possible [9, 11, 19, 20, 25]. Fluconazole, an echinocandin (usually caspofungin) or high-dose amphotericin B (3–5 mg/kg/day) was recommended for use in children in many of the included guidelines—dependent on previous antifungal exposure [9, 11, 15, 19, 25]. The included guidelines recommended that the duration of therapy in uncomplicated candidiasis be at least 14 days from either the last positive or the first negative blood culture [9, 11, 19, 25].

Invasive aspergillosis and other mould infections All guidelines covering invasive aspergillosis advised the use of voriconazole or high-dose liposomal amphotericin B (at least 3 mg/kg/day) as first-line therapy [11, 15, 19]. Echinocandins such as caspofungin were considered as acceptable alternatives [11, 15, 19]. Only one guideline gave recommendations on treatment duration; the Australasian guideline recommended consideration of response and immunological recovery [19].

Other confirmed invasive fungal diseases Various other guidelines provided recommendations for the appropriate antifungals in other invasive fungal diseases, including cryptococcosis, blastomycosis, histoplasmosis, sporotrichosis, mucormycosis, black fungi and rare invasive yeasts [11, 15, 17, 21–24, 26, 27].

Discussion

This review has appraised 19 guidelines produced by various international groups on the management of fungal infection in paediatric haematology and oncology. The quality of the included guidelines was variable. Only two guidelines met the pre-study definition of GOOD quality on the AGREE II assessment. There are many broad themes and recommendations that were consistent within the included guidelines though the specific details were, at times, contrasting. The quality of the guidelines did not dramatically impact on the recommendations given, except in relation to prophylaxis in the early stages of ALL treatment.

The guidelines gave clear and concise recommendations about prophylaxis in the paediatric haematology and oncology

setting with a substantial degree of concordance. Few guidelines drew attention to the fact that fluconazole does not provide cover against mould infection, and even fewer identified a need for environmental assessment for risk of mould infection. However, the use of itraconazole or posaconazole was advised in the majority of guidelines discussing prophylaxis and these agents would provide good mould cover in a high-risk group [9–15, 18].

In respect to empirical treatment, the guidance was much less precise, and there were few recommendations about when to stop treatment that was started for persistent fever. For pre-emptive treatment, we understand that further primary research is needed to identify whether this approach is appropriate within paediatric services.

The main strength of this work lies in the systematic searches for guidelines and the use of a structured appraisal tool to assess each guideline individually. This brings many of the strengths associated with systematic reviewing including explicitly demonstrating review methodology, identifying a breadth of research, reaching a clear understanding of the current knowledge, and a reduction in the bias involved in selecting included results. Furthermore, systematic searching and appraisal allows for identification of key areas for further research and development.

There is such a wide range in the quality of CPGs in this review that the review itself might be unseated by this feature. The guidelines generally have poorer quality rigour of development than was prospectively decided to be good and typically did not provide clear and detailed descriptions of their methodology. In addition to this, through limiting the review to English language guidelines, we may have missed CPGs in other languages, which may be of better quality than those included. The use of the ‘Guideline’ filter in MEDLINE may also have limited the search as it relies on guidelines being indexed appropriately. The impact of this limitation on the review is likely to be minimal given the extent of searching other sources alongside MEDLINE.

Taking into account these flaws, due to the consistency in the conclusions reached, we have been able to provide a clear summary of the current recommendations for antifungal therapy in paediatric haematology and oncology. We have been able to identify key similarities across studies of both good and poor quality and have also demonstrated repeated areas for further primary research. In particular, we have been able to explore the current guideline literature regarding antifungal prophylaxis in children.

The review of these guidelines has identified a series of guideline gaps in which key clinical questions are poorly addressed and require further recommendations to be made. These include the decision to discontinue empirical antifungal treatment in children, the relative benefits of empiric and pre-

emptive strategies and a clearer definition of risk strata which are agreed between guideline groups. Clarity in these areas could provide substantial patient and healthcare service benefits. Further work is also required to determine the most appropriate secondary prophylaxis for children and young people who have already been treated for a probable or proven invasive fungal disease. Furthermore, although not within the scope of this work, a review of guidelines or research surrounding the investigation of possible IFD, through imaging and laboratory investigations, may also be relevant to the paediatric haematology and oncology community.

Through demonstrating the areas where the current level of guidance is poor, we hope to inform further research such that future CPGs can progress from the current stance. In the meantime, paediatric haematology and oncology teams should work towards implementing the guidance where this proves to be similar across the current CPGs, specifically in regards to prophylactic therapy for children and young people at risk of fungal infections.

Future iterations of guidelines should consider working to published guideline production methodologies [30] and sharing summaries of evidence appraisal to reduce duplication of effort, within an international network such as the International Paediatric Oncology Guidelines in Supportive Care Network, improving the quality and efficiency of future clinical practice guidelines in this area. Guideline developers should consider reference to the AGREE II tool as a checklist for essential items to consider when writing their reports, paying particular attention to the systematic methods discussed in the rigour of development domain. Future guideline developers should also consider how to increase the applicability of the recommendations they produce.

Conclusions

Within this review we have critically appraised and analysed current published guidelines on antifungal therapy for paediatric haematology and oncology. The recommendations varied in regards to the strength of evidence behind them. Despite this, there were few areas of discrepancy. In areas where multiple guidelines exist, it may be sensible to use these techniques to assess the current discourse so as to focus future research and prevent replication of prior works.

There are many areas where the recommendations were clear about appropriate practice but further clarity is required, particularly the decision to discontinue empirical antifungal treatment in children, the relative benefits of empiric and pre-emptive strategies and a clearer definition of risk strata. We recommend the use of guideline production aids for future authors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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